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OUR EXPERIENCE WITH PEMETREXED/ CISPLATIN AS FIRST LINE CHEMOTHERAPY IN PATIENTS WITH ADVANCED NON- SQUAMOUS NON- SMALL CELL LUNG CANCER

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SUMMARY:

Objective: Lung cancer Pemetrexed is novel multitargeted antifolate which inhibits three key enzymes in the folate metabolic pathwaw. **Methods:** From May 2010 to March 2012 twenty two consecutive patients with morphologically proven advanced non- squamous non- small cell lung cancer entered the study. Treatment schedule consist of Pemetrexed 500 mg/m^2 on day 1 and Cisplatin 80 mg/m^2 with hyperhydratation administered as intravenous infusion with repetition every three weeks. Vitamins supplementation, antiemetics and Dexamethasone were administered too. **Results:** Overall response rate was 27,3 %, with one complete and five partial remissions obtained. The median time to progression and median overall survival time were 5,5 months and 9,6 months respectively. The main toxicity- grade 3 and 4, included neutropenia and diarrhea. **Conclusions:** That data suggest that chemotherapy with Pemetrexed / Cisplatin is reasonable choices for first- line chemotherapy in patients with inoperable non- squamous non- small cell lung cancer.

Key words: Pemetrexed, Cisplatin, Non- small cell lung cancer, First- line chemotherapy

Lung cancer is the most common cause of death from cancer among men and women in the word, resulting in approximately 221 130 new cases and 156 940 deaths in the United States in 2011 [1, 2]. Lung cancer causes nearly 1,3 million deaths per year worldwide. Non- small cell lung cancer (NSCLC) accounts for approximately 80- 85% of all cases of lung cancer. Surgery is the treatment of choice, but apparently 65% to 75% of patients with NSCLC have locally advanced stage III or metastatic stage IV disease. and are ineligible for curative surgery [3, 4]. The long- term prognosis for patients with advanced NSCLC remains poor, the 5- year survival rate ranging from 8% to 15% [5].

Combination chemotherapy is regarded as the standard treatment of patients with unresectable NSCLC. Some progress has been made in the treatment of advanced NSCLC during the past decades. Significant improvements in median survival in advanced NSCLC patients particularly in these with good performance status have been achieved with the use of Cisplatin- based regimens over best supportive care alone with 10% absolute improvement in the 1- year survival rate [6, 7]. The treatment options in NSCLC have changed significantly in the last years. The introduction of several new cytotoxic agents, including taxoids, Gemcitabine, and Vinorelbine, with novel mechanisms of action and less toxic than older therapies, offered hope for a better outcome because overall survival improved with combination regimens that included these new agents compared with Cisplatin alone [8]. Despite advances in the treatment in patients with inoperable NSCLC, the advent of third- generation cytotoxic has reached a therapeutic plateau [9]. There is thus a need for new agents, especially with different mechanisms of action, to improve cure rates and palliation for patients with advanced NSCLC.

Pemetrexed is a novel multitargeted antifolate. Its mechanism of action consists of the inhibition of three key enzymes in the folate metabolic pathway: thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase. These enzymes are involved in the synthesis of nucleotides, ultimately hindering RNA and DNA synthesis. Thus, the cytotoxicity of Pemetrexed is caused by inhibition of both the purine and pirimidine pathways [10]. Investigational studies have demonstrated the cytotoxic activity of this agent in a broad range of tumor types including NSCLC. These studies also showed that combinations of Pemetrexed with cisplatin, gemcitabine and taxanes produced additive or synergistic cytotoxicity [11]. Pemetrexed has favorable pharmacokinetic profile, and its mayor toxicity has been myelosupression. Recent studies showed that vitamin supplementation with B12 and folate reduced toxicity without nullifying the cytotoxic effects [12].

As a rule, the histologic subtype of NSCLC has not influenced the choice of chemotherapy. However, recent data demonstrate that expression of thymidylate synthase, the primary target for Pemetrexed, varies with the histologic subtype of NSCLC [13]. Expression of thymidylate synthase

is reported to be highest in squamous cancers, and clinical data suggest a differential response to Pemetrexed based on histologic subtype, supporting the latter biologic finding. Sigmond demonstrated that patients with high level of thymidylate synthase expression are less sensitive to Pemetrexed treatment [14]. In 2006 Ceppi and colleagues reported that squamous cell and high- grade carcinoma are related to higher thymidylate synthase expression levels, which should be considered when treating patients with thymidylate synthase- inhibiting agent [15]. This unfavorable effect on overall survival associated with squamous cell histology observed with Pemetrexed was also noted in a retrospective analysis of the single- agent trial of Pemetrexed versus docetaxel in patients with stage III/IV NSCLC after prior chemotherapy [16]. Peterson and colleagues showed that median overall survival and progression free survival in patients with non- squamous histology cancer treated with Pemetrexed was higher than in those with squamous histology (overall survival 9.2 months vs 6.2 months, hazard ratio 0.48, P< 0.001; progression free survival 3,4 versus 2,3, hazard ratio 0.56, p< 0.004) [17].

We design this study to gain clinical experience with Pemetrexed plus Cisplatin in chemotherapy- naïve patients with inoperable NSCLC. The objective of this study was to evaluate the efficacy and safety of Pemetrexed/ Cisplatin chemotherapy regimen in patients with advanced /stage III B - IV/ non- squamous NSCLC.

PATIENTS AND METHODS

Twenty two consecutive patients with NSCLC cancer, classified as stage IIIB or IV, entered the study. Participants needed to be between 18 and 75 years of age. Eligibility criteria included histologically or cytological confirmed non- squamous NSCLC. Other eligibility criteria were measurable or evaluable metastatic lesions of tumor, World Health Organisation /WHO/ performance status 0 to 2, life expectancy of minimum three months, no prior chemotherapy for lung cancer, adequate bone marrow reserve /absolute granulocyte count >1,5x10^9/L, platelet count >140x10^9/L/ as well as normal renal /serum creatinine level <1,5 cmol/L/ and hepatic function /serum bilirubin level <21 cmol/L/. Patients with progressive brain metastases, presence of active infections, or were unable to take folic acid, vitamin B_{12}, or corticosteroids were excluded from the trial.

Pemetrexed was supplied from commercial sources as a lyophilized powder in 500- mg vials and was reconstituted by adding 10 mL of 0,9% of sodium chloride. The appropriate dose of 500 mg/m^2 was infused intravenously over 60 minutes on day 1. Cisplatin 75 mg/m^2 was infused over 30 minutes with Mannitol diuresis and with hyperhydratation on day 1 too after Pemetrexed administration. This chemotherapy regimen was repeated every three weeks for six courses or until disease progression. Dexamethasone 4 mg was taken orally twice daily on the day, the day of, and the day after each dose of Pemetrexed. Folic acid supplementation at dose 350 to 1000 mcgr was taken orally daily beginning one week prior to the first dose of Pemetrexed and continued until three weeks after chemotherapy discontinuation. Vitamin B12 1000 ¼g was intramuscularly injected, starting one week prior to first dose of Pemetrexed and repeated every nine weeks until therapy discontinuation. All patients were given intravenous antiemetics prior chemotherapy- 5-hydroxytryptamine- 3- antagonist Ondasetron 8 mg.

Patients were retreated on this schedule if the absolute granulocyte count (AGC) was >1.5 × 10^9/l and platelets count was >100 × 10^9/l, and if the calculated creatinine clearance was >45 ml/ min. Dose reduction of 25% occurred if the nadir granulocyte count was <0.5 × 10^9/l and the nadir platelet count was ≥50 × 10^9/l, or if grade 2 mucositis occurred, after the previous course of Pemetrexed. A 50% dose reduction occurred if the nadir granulocyte count was ≥ 0.5 × 10^9/l, in association with a nadir platelet count of 25- 49 × 10^9/l, or if grade 3 or 4 mucositis occurred after the previous course of Pemetrexed. Once a dose reduction had occurred, it was not permitted to re- escalate for subsequent courses. In case of occurrence of grade 2 or greater cutaneous toxicity, the patient was to receive prophylactic oral dexamethasone in subsequent cycles at a dose of 4 mg b.d. from the day prior to treatment for a total of 3 days. If a patient experienced protracted neutropenia (i.e. grade 4 for >7 days) the granulocyte- colony stimulating factors were administered. In addition, if short- acting non- steroidal anti- inflammatory drugs (NSAIDs) were being taken, it was required that these medications be stopped for 3 days, commencing the day before treatment. If long- acting NSAIDs were being taken, it was required that these be stopped for seven days commencing five days before treatment with Pemetrexed.

Pretreatment evaluation included: a complete medical history, physical examination, complete blood cell counts, chemistry profile, urine analysis, chest x-ray, CT scans of the chest and, if necessary, of abdomen. A complete blood cell count was obtained before the start of each treatment cycle, together with a serum chemistry profile, abdomen ultrasound, physical examination, and toxicity assessment. Patients had radiological tumor parameter assessment before chemotherapy and on every three cycles. The tumor response classification was evaluated according to standard WHO response criteria (18). Response was defined as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). A CR was defined by the disappearance of all known disease, confirmed by two observations not less than 4 weeks apart. PR was defined as a decrease in tumour size of 50% or more (either measured or estimated in the case of measurable or assessable disease). In addition, there could be no appearance of any new lesions or progression of any known lesion(s). Objective tumour response (ORR) included both confirmed CR and PR. Stable disease was defined as no appearance of new areas of

disease or less than 25% increase in the described measurements. Tumor control included CR, PR and SD. Progressive disease was defined as increase with more than 25% of the measurements or appearance of new lesions.

The toxicities of each course were recorded prior to the commencement of the subsequent course, and were graded according to the WHO toxicity criteria [19].

The overall survival time was the time measured from study entry to death due to any cause. The duration of response was calculated from the day of the start of treatment to disease progression. The time to disease progression was calculated from study entry until the day of the first evidence of disease progression or death. The actuarial survival was estimated by the method of Kaplan and Meier [20].

RESULTS

Between February 2010 and March 2012, a total of 22 patients entered the study. The some baseline patient's characteristics are listed in Table 1. The median age was 61 years (range, 44-72 years), and there were 18 male and 4 female patients. Most patients had a good performance status, but four patients had ECOG performance status 2. Eight patients had stage IV tumors. Fourteen patients had adenocarcinoma and six patients had large- cell carcinoma. Two patients had undifferentiated carcinoma. The median interval from the primary diagnosis to the beginning of the treatment was 1,3 months. The follow- up period varied from 2 to 14 months (median 8 months). All twenty- two patients received at least one cycle of chemotherapy of Pemtrexed with Cisplatin. The total number of chemotheraphy cycles given was 103 while the median number of cycles received per patient was 4,5 (range 1- 6). Seven patients (31,9%) had dose modification at least in one cycle. The Pemetrexed dose was reduced due to adverse events in 4 patients and was delayed (mostly due to adverse events) in 5 patients. At the end of the follow- up in October 2012, no patients were lost to follow- up and 4 patients were still alive.

Efficacy

The resulting antitumor effects are presented in Table 2. Of the 22 patients treated with Pemetrexed with Platinum, one CR were observed, whereas five patients achieved PR. The objective response rate (ORR= CR+ PR) was 27,3%. In the remaining patients, eleven (50, 0%) achieved SD and five (22,7%) had PD. Thus, the disease control rate (DCR= CR+ PR+ SD) in this study was 77,3%. The median time to progression of disease was 5,5 months and the overall survival time was 9,6 months. The 1-year survival rate was 31, 9%.

Toxicity

A total of 104 chemotherapy cycles were delivered to all 22 patients. Toxicity was evaluated in all patients and in all cycles, 17 patients (77,27% of those treated) reported at least one adverse event during the study, 7 patients (31,8%) and 6 patients (27,2%) experienced grade 3 and grade 4 adverse events, respectively.

Hematologic toxicity is summarized in Table 3. The most common adverse event was granulocytopenia. Grade 3 or 4 neutropenia was observed in 4 patients (18,2%), but there was only one episode of febrile neutropenia (4,6% of all treated). Thrombocytopenia was rare and a platelet count below $25x10^9$/L was observed in only one patient (4,6% of all treated). Anemia grade 3- 4 was not observed.

Non-hematologic toxicity is displayed in Table 4. Grade 3 or 4 nausea or vomiting was observed in only two patients (18,2%), and three patients experienced grade 3 or 4 diarrhea (13,6%),. Five patients developed rush (22,7%), but this was of grade 3 or 4 in only two patients (9,1%).

DISCUSSION

The last two decades we have seen the introduction of several new chemotherapeutic agents such as gemcitabine, the taxanes- paclitaxel and docetaxel, and vinorelbine, that have activity against NSCLC and that produce single- agent response rates of greater than or equal to 20% in previously untreated patients with advanced tumors. Response rates for the new agents in combination with cisplatin usually have ranged from 30–40% or higher, and randomized trials comparing chemotherapy combinations using these new agents uniformly have reported median survival times of approximately 8- 10 months and 1- year survival rates in the range of 30% to 40% [21].

Pemetrexed is a novel multi- targeted antifolate chemotherapy agent. In 2008 Scagliotti et al. [22] showed that patients with non- squamous tumors had significant improvement in overall survival. Patients in the Cisplatin/ Pemetrexed arm with adenocarcinoma and large- cell carcinoma had significantly better survival than patients in Cisplatin/ Gemcitabine arm. Median survival in both arms was 10,3 months. However, when comparing by histology type, significant differences were seen between the two arms in patients with adenocarcinoma and large- cell carcinoma: those with adenocarcinoma who were randomized to Cisplatin/ Pemetrexed had a median survival of 12,6 months versus 10,9 months for those in the Cisplatin/ Gemcitabine arm (p=0.03). In patients with large- cell carcinoma, patients randomized to Cisplatin/ Pemetrexed had a median survival of 10,4 months versus 6,7 months for the Cisplatin/ Gemcitabine arm. One potential explanation may relate to the thymidylate sinthase expression levels in NSCLC histology types. Preclinical data have indicated that overexpression of thymidylate sinthase correlates with reduced sensitivity to Pemetrexed [23, 24]. Based on this study Pemetrexed has been granted as the first- line treatment for patients with advanced non- squamous NSCLC.

The aim of our study was to explore the efficacy and safety of Pemetrexed/ Cisplatin chemotherapy regimen as

first- line therapy in patients with advanced /stage IIIB- IV/ non- squamous NSCLC. Our results are similar to those reported by Scagliotti. We observed median survival time of 9,6 months with ORR 27,7 %. Our results are also similar to the results of Norwegian phase III study assessed the Pemetrexed/ Carboplatin compared with Gemcitabine/ Carboplatin as first- line chemotherapy in advanced NSCLC. In this trial there was no difference in median OS time between treatment groups (Pemetrexed/ Carboplatin- 7,3 months, Gemcitabine/ Carboplatin- 7,0 months, p= 0, 63). The incidence of grades 3- 4 toxicities are similar to those reported too. The main hematological toxicity neutropenia was observed in 18,2% of our patients compared with 15,1% of patients in Scagliotti and 40% of patients in Norwegian trial. Cutaneous toxicity was less frequent in the current study with grade 3-4 observed in only 9% of patients, due to the routine adoption of prophylactic oral Dexamethasone administration and Vitamine B12 and Folic acid supplementation.

In conclusions, our results suggest that Cisplatin/ Pemetrexed chemotherapy provides activity that is similar to that observed when Cisplatin is combined with standard regimens [21]. Cisplatin/ Pemetrexed regimen has similar OS time, better tolerability and more convenient administration than Cisplatin/ Gemcitabine regimen, for first- line treatment of patients with advanced or metastatic nonsquamous NSCLC. Further research is warranted to investigate whether biomarker status (thymidylate sinthase expression levels) can help to identify the patients who will benefit from Pemetrexed therapy.

Table 1. Patient characteristics

Patient characteristics	Number of patients- 22
Age (years)	44 – 72
Sex Males Females	 18 (81,8%) 4 (18,2%)
Dominant site of metastasis Pleura Liver	 7 (31,9%) 5 (22,7%)
Lung Bone Soft tissue Performance status WHO 0 1 2	2 (9,0%) 1 (4,5%) 7 (31,9%) 11 (50,0%) 7 (31,9%) 4 (18,2%)
Stage III IV Histology	 14 (63,6%) 8(36,4%)
Adenocarcinoma Large- cell Undifferentiated	14 (63,6%) 6 (27,3%) 2 (9,1%)

Table 2. Objective responses

Patients/ Response	CR	PR	NC	PD	ORR %
22	1	5	11	5	27,3%

ORR= CR+ PR

CR - Complete response; PR - Partial response; NC - No change; PD - Progressive disease; ORR - Overall response rates;

Table 3. Hematological toxicity- grade 3- 4

Adverse drug reactions	Number of patients
Neutropenia	4 (18,2%)
Febrile neutropenia	1 (4,6%)
Thrombocytopenia	1 (4,6%)

Table 4. Non-hematologic toxicity- grade 3- 4

Adverse drug reactions	Number of patients
Diarrhea	3 (13,6%)
Nausea	2 (9,1%)
Rush	2 (9,1%)

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